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In re Patent Application of)
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Philippe DIAZ et al.) Group Art Unit: 1654
)
Application No. 09/379,308) Examiner: D. Lukton
)
Filed: August 23, 1999)
)
For: HETEROCYCLIC COMPOUNDS,)
PHARMACEUTICAL AND COSMETIC)
COMPOSITIONS CONTAINING THEM)
AND USES THEREOF)

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10-3-00

Declaration considered - D. Lukton 3/25/01

DECLARATION BY MICHEL DEMARCHEZ PURSUANT TO 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, MICHEL DEMARCHEZ, declare and state as follows:

(1) I reside at 154, Chemin Saint Michel, 06 620 Le Bar sur Loup, France.

(2) I have a Ph.D. in Cell Biology.

(3) I have been employed by CIRD Galderma from October 1, 1982 to the present date. My current title is Research Director.

(4) Based on my job title and duties, I can attest to the fact that the experiments discussed below were conducted which clearly demonstrate that several compounds of the present invention have biological activity as RAR type agonists or RXR agonists.

(5) The fact that the compounds according to the invention comprise therapeutic utility is further substantiated by data which has been obtained by the present inventors relating to several compounds according to the invention. Specifically, in a biological test, i.e., the F9 test which is an accepted assay for identifying RAR-type agonists described in *Skin Pharmacology*, 1990, 3, 256-267, the present inventors have demonstrated that the compounds of Example 2 and Example 6 are RAR-type agonists. These findings are supported by the results shown in Table 1 below:

Table 1

Compounds	AC 50 (nM)
Example 2	2000
Example 6	1900

In Table 1, AC 50 indicates the retinoid concentration inducing 50% of plasminogen production relative to the maximum of the dose-response curve.

Moreover, in another accepted assay, described in Levin et al, *Nature*, Vol 355, pp. 359-361 (1992), and in Allenby et al, *Proc. Natl. Acad. Sci. USA*, Vol. 90, pp. 30-34 (1993), the inventors confirmed that the compounds of Example 2 and

Example 4 function as RXR agonists. The results illustrating how compounds according to the invention can be RXR agonists are summarized in Table 2 below:

Table 2

Compounds	RXR Binding Ki (nM)	RXR transactivation test (%)	RXR transactivation AC 50 (nM)
Example 2	1048	39	712
Example 4	5387	56	479

It should be noted that the compound of Example 2 is active both as an RAR and as an RXR agonist. Thus this compound is a panagonist compound.

(6) Moreover, it should be noted that evidence that retinoids find established utility as therapeutic agents is amply documented through the references provided herewith disclosing the use of retinoids for treatment of conditions including dry eye disorders, cancer, skin cancer specifically, cervical cancer, prevention of skin cancer, and disorders involving cell proliferation and differentiation. These references substantiate that retinoid compounds including RAR receptors, RAR agonists and RXR agonists find accepted usage as therapeutic agents.

In particular, Safonova et al, *Biochemical and Biophysical Research Communications*, Vol. 204, No. 2, 1994, discloses the usage of such agonists on cell differentiation and potential therapeutic utility. Moreover, Hong et al, *Retinoids and*

Human Cancer, from *The Retinoids: Biology, Chemistry, and Medicine*, 2 nd Ed., 1994, reviews the accepted usage of retinoids in the treatment of human cancer. The reference identifies numerous retinoids having such utility including all-trans retinoic acid, isotretoin, etretinate, fenretinide, and arotinoids. Also, Lippman and DiGiovanna, *Retinoids and Skin Cancer*, teache the potential usage of retinoids in treating such disorder and the use of single agent retinoid therapies in advanced malignant diseases such as acute promyelocytic leukemia, mycosis fungoides, and skin cancer. The authors indicate that retinoids show great therapeutic promise in such treatments.

Also, Kavanagh et al, *Retinoids and Cervical Cancer*, disclose that topical trans-retinoic acid is active in the treatment of cervical carcinogenesis with complete lesion reversal obtained in one trial. In particular, special reference is made to Table 2 of the Kavanagh document, which summarizes the results of studies of local retinoid activity and toxicity in the treatment of cervical displasia. Still further, Meyskens et al, *Role of topical tretinoin in melanoma and dysplastic nevi*, Vol. 15, No. 4 (1986), discloses the usage of topical tretinoin in the treatment of melanoma and dysplastic nevi, with the authors concluding that such administration had activity against melanoma, and its precursor conditions.

(7) Therefore, as discussed above, and as established by the references

provided herewith, it is known in the art that such agonists find accepted usage as pharmacological agents, in particular for treatment of disorders involving cell proliferation and differentiation and especially keratinization related disorders. Thus, it is reasonable to conclude that the compounds of the subject invention, with their demonstrated RXR or RAR activity will likewise exhibit pharmacological properties.

Moreover, to more specifically illustrate the *in vivo* activity of compounds according to the present invention, the inventors conducted *in vivo* assays that show the retinoic activity of compounds according to the invention.

More specifically, retinoic activity of compounds according to the invention has further been demonstrated in an *in vivo* assay which measures the effect of compounds according to the invention on ear oedema induced by topical administration of a compound according to the invention, specifically the compound of Example 2. Table 3 shows the % of augmentation of the ear oedema induced by a topical administration of the compound of Example 2:

Table 3

Concentration of Example 2	% of Augmentation of the ear Oedema
0.1%	9%
0.3%	5%
1%	37%

These results amply support the retinoic activity of the compound of Example 2.

(8) Therefore, based on my knowledge and expertise in this technical area, and in view of the above-obtained results, it is reasonable to conclude that the efficacy of retinoid compounds as pharmaceutical agents is accepted in the art. Therefore, based on the data demonstrating that compounds according to the invention function as RAR and RXR agonists, it is reasonable to conclude that they will exhibit desirable pharmacological properties and will be useful in the treatment of the recited conditions. Also, based on the *in* vitro and in *vivo* data discussed above, it is reasonable to conclude that compounds according to the invention may be used in treatment of the recited conditions, in particular treatment of dermatological conditions such as those associated with differentiation and proliferation.

(9) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

September 1, 2000
DATE

Michel Demarchez
MICHEL DEMARCHEZ, Ph.D.